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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	**PAPER NUMBER**
1631	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

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Office Action Summary	Application No.	Applicant(s)
	10/826,153	SCHER ET AL.
	Examiner	Art Unit
	Russell S. Negin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *1-25 and 49-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/19/04*.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group II (claims 26-48) in the reply filed on 30 August 2006 is acknowledged.

Claim 1-25 and 49-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 30 August 2006.

Applicant's election with traverse of a single species within each of eleven Markush groups in Group II in the reply filed on 30 August 2006 is acknowledged. The traversal is on the ground(s) that the requirement of serious burden has not been met. This is not found persuasive because each of the eleven Markush Groups covers a broad range of species relating to nanocrystals and their applications and measurements; searching all of the species would require undue burden in all eleven circumstances.

The requirement is still deemed proper and is therefore made FINAL.

The result of the eleven species elections does not further limit the number of claims examined in the application. Accordingly, claims 26-48 are examined in the current application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must make CdSe in a nanocrystal with a nonvisible emission spectrum. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) While the disclosure provides guidance on the fact that CdSe is a possible nanocrystal, it does not provide specific guidance on how to produce a nonvisible

spectrum using CdSe nanocrystals.

c) While the disclosure provides examples of how to use the invention in general, it does not provide specific guidance on how to produce a nonvisible spectrum using CdSe nanocrystals.

d) The nature of the invention, nanocrystal analysis, is complex.

e) The prior art does not show nonvisible spectra using CdSe. The invention of Bruchez et al. [US Patent 6,274,323] states in column 17, lines 25-27, "semiconductor nanocrystals that emit energy in the visible range include, but are not limited to CdS, CdSe, CdTe, ZnSe, ZnTe, GaP, and GaAs."

f) The skill of those in the art of nanocrystal analysis is high.

g) There is unpredictability of the ability to generate nonvisible emission spectra using CdSe.

h) The claims are broad in that they are drawn to any nonvisible emission spectra using CdSe.

The skilled practitioner would first turn to the instant description for guidance in using the claimed invention. However, the description lacks clear evidence that CdSe can generate a nonvisible spectrum. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art states that CdSe produces visible spectra. Finally, said practitioner would turn to trial and error experimentation to make a CdSe nanocrystal with a nonvisible spectrum. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 26-29, 31-32, 34-37, 40, 43, and 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zaheer et al. [Nature Biotechnology, volume 19, December 2001, pages 1148-1154] in view of Bruchez et al. [US Patent 6,274,323, issued August 14, 2001].

Claim 26 claims a composition of a population of nanocrystals comprising an excitation with portion in the nonvisible ranges and an emission spectrum that is in the nonvisible range. The nanocrystal is either in an adherent matrix or is suspended in liquid and is suitable for administration into a mammal.

Claim 27 limits claim 26 to a semiconductor.

Claims 28-29 limit the size of the nanocrystal.

Claim 31 compares the band gaps of the inner and outer core.

Claim 32 claims that the nanocrystals comprise InP.

Claim 34 limits claim 26 wherein the population of nanocrystals comprises two or more subsets of nanocrystals.

Claim 35 limits the crystal spectral line width to specific constraints.

Claim 36 limits claim 26 to where the nanocrystals are manufactures by colloidal synthesis/

Claim 37 dictates the possible wavelengths of the excitation spectra.

Claim 40 limits the emission spectra to ultraviolet wavelengths.

Claim 43 limits claim 26 wherein delivery to the mammal comprises intravenous delivery.

Claim 46 limits claim 26 wherein the nanocrystal adherent matrix is a polymer.

Claim 47 limits claim 26 wherein the composition is excitable through a barrier.

Claim 48 limits claim 47 to where the barrier is an animal.

The article of Zaheer et al., entitled, "In vivo near-infrared fluorescent imaging of osteoblastic activity," states in the last two sentences of the abstract:

> We have synthesized a near infrared (NIR) fluorescent biphosphonate derivative that exhibits rapid and specific binding to HA [hydroxyapatite] in vitro and in vivo. We demonstrate NIR light-based detection of osteoblastic activity in a living animal, and discuss how this technology can be used to study skeletal, osteoblastic metastasis, coronary atherosclerosis, and other human diseases.

The emissions and excitation spectra of the dyes IRDye78 and Pam78 are illustrated in Figure 1D of Zaheer et al. on page 1149. In both plots of Figure 1D, the

emissions spectra are entirely nonvisible (dashed lines) while the excitation spectra are partially nonvisible (solid lines). Figures 3A and 3B on page 1151 illustrate the result of an intravenous injection of the dyes into a mammal (mice).

Zaheer et al. claim three advantages of using dyes with nonvisible emissions: (bottom of column 1 on page 1148)

> First, the photon penetration into, and out of, tissue is high. Second, tissue absorption and autofluorescence is minimized, yielding an inherently high contrast between target and background. Third, optical scatter within tissue is lower.

However, while Zaheer et al. teaches the use of dyes with the appropriate wavelengths for analysis in mice (in vivo), Zaheer et al. does not teach use of semiconductor nanocrystals to accomplish this goal.

The invention of Bruchez et al., entitled, "Method of detecting an analyte in a sample using semiconductor nanoanalysis as a detectable label," states in its abstract:

> The use of semiconductor nanocrystals as detectable labels in various chemical and biological applications is disclosed. The methods find use for detecting a single analyte, as well as multiple analytes by using more than one semiconductor nanocrystal as a detectable label, each of which emits at a distinct wavelength.

The term "semiconductor nanocrystal" is defined in column 8 of Bruchez et al., lines 59-65:

> The terms "semiconductor nanocrystal," "quantum dot," and "QdotTM nanocrystal" are used interchangeably herein and refer to an inorganic crystallite between about 1 nm and about 10000 nm in diameter or any integer or fraction of an integer therebetween, preferably between about 2 nm and about 50 nm...

The use of the required species of InP in a nonvisible emission spectrum is described in column 17, lines 28-32, of Bruchez et al. which states:

> Semiconductor nanocrystals that emit energy in the near IR range include, but are not limited to, InP, InAs, InSp, PbS, and PbSe. Finally, semiconductor nanocrystals that emit energy in the blue and near-ultraviolet include, but are not limited to ZnS, and GaN.

Excitation spectra are described in column 5, lines 9-14 of Bruchez et al. which state:

> In addition the range of excitation wavelengths of such nanocrystals is broad and can be higher in energy than the emission wavelengths of all available semiconductor nanocrystals. Consequently, this allows the use of a single energy source, such as light, usually in the ultraviolet or blue region of the spectrum...

Concerning spectra, Bruchez et al. expand the discussion in column 20 lines 27-33 by stating:

> Likewise, for semiconductor nanocrystals producing emissions in the infrared or ultraviolet regions, the characteristic wavelengths that the discrete optical transitions occur at provide information about the identity of the particular semiconductor nanocrystal, and hence about the identity of or location of the analyte of interest.

On the subject of spectral widths and bandgaps energies, Bruchez et al. states in column 18, lines 1-5 and lines 19-23:

> However, for some applications high information density will not be required and it may be more economically attractive to use more polydisperse particles. Thus, for applications that do not require high information density, the linewidth of the emission may be in the range of 40-60 nm.

The use of multiple populations of nanocrystals is described in column 19 lines 23-26 of Bruchez et al.

> The above method can be used to prepare separate populations of semiconductor nanocrystals, wherein each population exhibits a different characteristic photoluminescence spectrum.

Bruchez et al. mention a possible use of their invention as an in vitro indicator in column 3, lines 55-58, "Radiolabels molecules and compounds are frequently used to detect biological compounds both in vitro and in vivo."

While Bruchez et al. do not describe in vivo use in mammals, ex vivo use of nanocrystals in biopsies of tissue is described in example 17 in column 534, lines 1-20, entitled, "Tissue microarrays for high-throughput immunohistochemcial staining of tumor specimens."

It would have been obvious for someone of ordinary skill in the art at the time of the instant invention to modify the in vivo study of nonvisibly emitting dyes in mice of Zaheer et al. in view of the nanocrystal study of Bruchez et al., because while Zaheer et al. teaches three reasons to use nonvisibly emitting dyes (photon penetration, tissue absorption, and contrast), Bruchez et al. shows advantages of making and using nanocrystals in the form of mixtures of different nanocrystals because each species emits at a distinct wavelength (i.e. see portion of abstract of Bruchez et al. cited on page 7 of this Office action); the application of nanocrystal mixtures is useful in biological applications such as biopsies.

Claims 26, 30 and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zaheer et al. in view of Bruchez et al. as applied to claims 26-29, 31-32, 34-37, 40, 43, and 46-48 above, and further in view of Bruchez et al. [Science, volume 281, 1998, pages 2013-2016, In formation Disclosure Statement, source CA, 19 October 2004]. This second Bruchez reference will be referred to as "Bruchez et al. (1998)."

Claim 30 limits the production of the nanocrystals to usage of substitutes silanes.

Claim 38 limits claim 26 to a population of nanocrystals comprising two or more subsets of crystals with different light excitation wavelengths.

Claim 39 limits claim 38 to wavelengths that are alternately excited with different excitation wavelengths.

While Zaheer et al. in view of Bruchez et al. teach in vivo use of nanocrystal solutions in mammals, they do not teach use of silanes and multiple excitation wavelengths.

The article of Bruchez et al. (1998), entitled, "Semiconductor nanocrystals as fluorescent biological labels," states in the abstract:

> Semiconductor nanocrystals were prepared for use as fluorescent probes in biological staining and diagnostics. Compared with conventional fluorophores, the nanocrystals have a narrow, tunable, symmetric emission spectrum and are photochemically stable. The advantages of the broad, continuous excitation spectrum were demonstrated in the dual emission, single excitation labeling experiment on mouse fibroblasts. These nanocrystal probes are thus complementary and in some cases may be superior to existing fluorophroes.

Figures 1 and 2 on page 2014 of Bruchez et al. (1998) illustrate the excitation and emission spectra meeting the requirements of being partially in the nonvisible range. Figure 2 shows twelve emission spectra (each sigmoidal curve corresponds to a single spectrum- each spectrum corresponding to a specific nanocrystal size and molecule). For example, the four leftmost spectra in Figure 2A of Bruchez et al. are red in the original article and correspond to the nanocrystal InAs at sizes 2.8, 3.6, 4.6, and 6.0 nm, respectively (from left to right). The next rightmost are green in the original article and correspond to the crystal InP at sizes 3.0 3.5, and 4.6 nm (from left to right). The rightmost spectra are blue in the original article and correspond to the crystal CdSe at sizes 2.8, 3.6, 4.6, and 6.0 nm, respectively. Consequently, Figure 2 of Bruchez et al. (1998) illustrates the multiple emission wavelengths.

Figure 2 shows more that one light emission wavelength distribution with the appropriate spectral widths (about 25 to 30 nm) illustrated in the figure. Figure 1 of Bruchez et al. (1998) illustrate more than one excitation wavelength. There is more

than one excitation peak in Figure 1B, corresponding to different excitation wavelengths alternately.

Bruchez et al (1998) ends the article by stating:

> The development of nanocrystals for biological labeling opens up new possibilities for many multicolor experiments and diagnostics. Further, it established a class of fluorescent probe for which no small organic molecule equivalent exists. The tunability of the optical features allows for their use as direct probes or as sensitizers for traditional probes. These nanocrystals have long fluorescent lifetimes (hundreds of nanoseconds), which can allow for time-gated detection for autofluorescence suppression. Further development, such as direct immunolabeling, in situ hybridization, and incorporation into microspheres will be important for applications such as cytometry and immunocytobiology. In addition nanocrystal probes may prove useful for other contrast mechanisms such as x-ray fluorescence, x-ray absorption, electron microscopy, and scintillation proximity imaging, and the use if for-red or infrared-emitting nanocrystals (InP and InAs) as tunable, robust infrared dyes is another possibility.

Footnote number 20 on page 2015 of Bruchez et al. (1998) shows how the nanocrystals are synthesized using substituted silanes and the formation of polymers (footnotes 20 and 22). Use of silanes is a widely accepted procedure for generating nanocrystals.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the inventions of Zaheer et al. in view of Bruchez et al. as applied to claims 26-29, 31-32, 34-37, 40, 43, and 46-48 above, and further in view of Bruchez et al. (1998) because Bruchez et al. (1998) has the advantage of improving a common technique in the art (use of silanes to make nanocrystals) to generate the nanocrystals with tunable wavelengths; this improvement results in better performance of biological measurement techniques (i.e. X-ray fluorescence, x-ray absorption, and scintillation proximity imaging).

Claims 26, 41-42, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zaheer et al. in view of Bruchez et al. as applied to claims 26-29, 31-32, 34-37, 40, 43, and 46-48 above, and further in view of Weiss et al. [WO 00/55631].

Claim 41 limits claim 26 wherein a subset of the nanocrystals comprises a predetermined intensity of emission at a wavelength.

Claim 42 limits claim 41 to where the intensity is predetermined by varying concentration of a nanocrystal constituent.

Claim 44 limits claim 26 wherein the population of nanocrystals comprises a predetermined excitation spectra or emission spectra.

Claim 45 limits claim 44 by varying the size of the nanocrystal.

While Zaheer et al. in view of Bruchez et al. teach in vivo use of nanocrystal solutions in mammals, they do not teach variance of concentration of a constituent and its effects on spectra.

The patent of Weiss et al., entitled, "Semiconductor nanocrystal probes for biological applications," states on page 14, lines 14-20:

> Furthermore, the frequency and wavelength of the narrow wavelength band of light emitted form the semiconductor nanocrystal may be further selected according to the physical properties, such as size, of the semiconductor nanocrystal. The wavelength band of light emitted by the semiconductor nanocrystal, formed using the above embodiment, may be determined by either (1) the size of the core, or (2) the size of the core and the size of the shell...

On page 15, lines 5-12, Weiss et al. states, "Selection of the emission wavelength by varying the composition, or alloy, of the semiconductor nanocrystal is old in the art. As an illustration, when CdS semiconductor nanocrystal, having an emission

wavelength of 400 nm, may be alloyed with a CdSe semiconductor nanocrystal, having an emission wavelength of 530 nm."

On page 53, lines 12-28, Weiss et al. explains the advantages of using their semiconductor nanocrystals:

> Thus, the invention provides an semiconductor nanocrystal probe containing a semiconductor nanocrystal capable, upon excitation by either electromagnetic radiation (of either narrow or broad bandwidth) or particle beam, of emitting electromagnetic radiation in a narrow wavelength band and/or absorbing energy and/or scattering or diffracting said excitation, thus permitting the simultaneous usage of a number of such probes emitting different wavelengths of electromagnetic radiation to thereby permit simultaneous detection of the presence of a number of detectable substances in a given material. The probe material is stable in the presence of light or oxygen, capable of being excited by energy over a wide spectrum, and has a narrow band of emission, resulting in an improved material and process for the simultaneous and/or sequential detection of a number of detectable substances in a material such as a biological material.

It would have been obvious at the time of the instant invention for someone of ordinary skill in the art to practice the inventions of Zaheer et al. in view of Bruchez et al. as applied to claims 26-29, 31-32, 34-37, 40, 43, and 46-48 above, and further in view of Weiss et al. [WO 00/55631] because Weiss et al. has the advantage of detecting multiple substances simultaneously using a given wavelength of excitation relevant to biological applications.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Andrew Wang, Supervisory Patent Examiner, can be reached at (571) 272-0811.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Yolanda Chadwick, whose telephone number is (571) 272-0514.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RSN
6 December 2006

6 December 2006

7 December 2006

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER